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Continuous Infusion of Porcine Factor VIII in the Management of Patients With Factor VIII Inhibitors

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The effectiveness of continuous infusion porcine factor VIII (PFVIII) has been evaluated in the treatment of 7 consecutive patients with factor VIII(FVIII) inhibitors. Two patients had hemophilia A and five were nonhemophiliacs with acquired FVIII inhibitors. The median pretreatment anti-porcine FVIII titre was 0.2 (range: 0–15.0) Bethesda units (BU), and the anti-human FVIII titer was 12.0 BU (range: 2.4–50.0). All patients presented with major bleeding. Patients were given a bolus dose of PFVIII followed by continuous infusion. Six patients also received immunosuppressive therapy. Therapeutic FVIII levels (>0.5 U/ml) were achieved in 6 of 7 patients at a median time of 12.5 hr, and then maintained with continuous infusion PFVIII. Six patients were treated for more than 7 days, and in four of these there was a decline in FVIII recovery between days 7 to 11, presumably related to a rising antibody response to PFVIII. These four patients were plasmapheresed and the three patients with autoantibodies recovered therapeutic FVIII levels but this did not occur in the patient with hemophilia. Thrombocytopenia developed in 4 patients at days 18 to 24, with the platelet count falling to 11 to 87 × 10^9/L, and the PFVIII was discontinued in 3 patients. All patients recovered from the acute bleeding events. With prolonged immunosuppressive therapy, the FVIII inhibitor disappeared in all patients with autoantibodies and there have been no relapses after a median follow-up period of 581 days. This study demonstrates that continuous infusion PFVIII is an effective therapy for patients with FVIII inhibitors, but that prolonged treatment is associated with the development of inhibitors to porcine FVIII and severe thrombocytopenia, which readily corrects with discontinuation of PFVIII. Am. J. Hematol. 56:112–118, 1997.

Key words: factor VIII inhibitors; hemophilia A; porcine FVIII; continuous infusion

INTRODUCTION

Inhibitors to FVIII are a rare occurrence, and may develop in patients with hemophilia A who receive exogenous FVIII products (alloantibodies) or may occur spontaneously in non-hemophiliacs (autoantibodies). The incidence of inhibitors in hemophilia A ranges between 5–20% [1,2] while the incidence of spontaneously acquired inhibitors in the population is 0.2–1 per million/year [3]. In patients with hemophilia, inhibitor formation is more frequent in those with severe disease, and generally occurs at a young age. A genetic predisposition to alloantibody formation is suspected, and FVIII products may vary in their propensity to induce inhibitor formation [1,2]. In non-hemophiliacs, the acquired inhibitors occur most often in patients over 60 years of age, sometimes in association with an autoimmune disorder, drug therapy with penicillin, or hematologic malignancies, or during pregnancy.

Patients with FVIII inhibitors commonly present with an overt bleeding diathesis and dramatic hemorrhages into soft tissues, hematuria, hematemesis, or postpartum bleeds. The mortality associated with this condition is significant and may be as high as 10–22% in acquired

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TABLE I. Patient Characteristics

UPN[a]	Type of inhibitor	Age	Sex	Clinical presentation	Baseline laboratory data		
					FVIII levels (U/ml)	Inhibitor titers (BU/ml)	
						Anti-human	Anti-porcine
1	ALLO-	46	M	Upper gastrointestinal bleeding	<0.01	50.0	15.0
2	ALLO-	38	M	Subdural spinal hematoma	<0.01	12.0	2.0
3	AUTO-	77	F	Compartment syndrome right arm	0.06	10.5	0.2
4	AUTO-	80	M	Extensive ecchymosis upper trunk and right groin	0.02	17.0	0.8
5	AUTO-	72	M	Right elbow and left thigh ecchymosis	0.10	4.5	0
6	AUTO-	65	F	Compartment syndrome right arm	0.03	12.5	0
7	AUTO-	63	M	Gross hematuria	0.09	2.4	0

[a]Unique patient number.

hemophilia [3]. The treatment of these patients is complex, requiring clinical expertise and significant resources [4–7]. For patients who are bleeding, hemostasis can be accomplished through administration of FVIII concentrates or products that activate the clotting cascade without the need of FVIII. Examples of the latter include prothrombin complex concentrates and recombinant factor VIIa [8,9]. Heterologous FVIII concentrates, e.g., porcine FVIII, may also be used because of the lower cross-reactivity with human FVIII inhibitor [7,10]. An advantage of PFVIII, as opposed to recombinant factor VIIa or prothrombin complex concentrates, is the ability to measure FVIII recovery as an assessment of hemostatic control. Porcine FVIII concentrate (Hyate:C®, Speywood Pharmaceuticals Ltd., WREXHAM, U.K.), the only non-human FVIII product commercially available, has been successfully used to manage patients with FVIII inhibitors [4,5,10–12]. Early problems with this product, including allergic reactions and thrombocytopenia [13,14], were reduced with the introduction of a polyelectrolyte-fractionated formulation in 1981.

In vitro studies have shown that PFVIII is stable when diluted in normal saline at concentrations of 15 and 30 U/ml at room or body temperature for 24 hr. Stability for 24 hr was maintained at room temperature even at concentrations of 5 U/ml [15]. Patients with FVIII inhibitors have been treated with PFVIII (Hyate:C) by continuous infusion and initial results suggest that this is a feasible and cost-effective treatment [16]. In the present report, we describe our experience with the use of continuous infusion PFVIII in the management of 7 consecutive patients with FVIII inhibitors.

PATIENTS AND METHODS

Patients

Seven consecutive patients with FVIII inhibitors and bleeding diatheses presented to our service during the period of October 1993 and December 1995. Two patients had severe hemophilia A with inhibitors and five had spontaneously acquired FVIII inhibitors. Patient characteristics are detailed in Table I. Initial laboratory data included the measurement of factor FVIII level, and the level of FVIII inhibitors against both human and porcine FVIII.

The median FVIII level measured 0.06 U/ml (range: 0.02–0.10) in patients with FVIII autoantibodies and <0.01 U/ml in the hemophiliacs. In patients with autoantibodies, the median inhibitor titer against human FVIII was 10.5 BU (range: 2.4–17.0), but inhibitory titers against porcine FVIII were undetectable in most patients (range: 0–0.8 BU). Patients with alloantibodies also had lower inhibitor titers to porcine than human FVIII (Table I).

Factor VIII Measurement

Dilutions of patient plasma were compared with dilutions of a normal pooled plasma in a one-stage kaolin-activated partial thromboplastin time (a PTT)-based assay using human Factor VIII-deficient substrate plasma (Organon Teknika, Durham, NC).

Factor VIII Inhibitor Assays

Neutralizing antibodies to both human and PFVIII were measured by the standard Bethesda assay [17]. Either normal human pooled plasma or PFVIII concentrate (diluted with sterile water to a concentration of 1 IU/ml) was mixed with an equal volume of patient plasma and incubated at 37°C for 2 hr. Residual factor VIII was then measured and the inhibitory levels were expressed as Bethesda units (BU).

Reconstitution of PFVIII for Continuous Infusion

Porcine FVIII (Hyate:C®) was reconstituted in sterile water (20 ml/vial) according to the manufacturer's recommendations. This was further diluted with an equal volume of 0.9% sodium chloride reaching a final concentration of ≥5 U/ml. The solution was administered as a continuous infusion through a Buretrol® and polyvinylchloride intravenous tubing (Baxter Corp., Toronto). Enough product was diluted each time to provide for 4–8 hr of infusion. These concentrations of PFVIII have been

shown to retain FVIII activity within 90% of baseline values for at least 24 hr following preparation, when the diluted product is stored at room temperature [15].

RESULTS

Clinical Outcome

All patients received an initial bolus of PFVIII (20–76 U/kg) to achieve hemostatic FVIII levels, followed by continuous infusion of PFVIII in doses ranging from 4–12 U/kg/hr. Repeated bolus doses and adjustments to the continuous infusion were made as required to achieve a therapeutic FVIII level (>0.5 U/ml). The median duration of PFVIII treatment was 18 days (range: 3–22). A total of 105 continuous infusion PFVIII treatment days was given. The median total quantity of PFVIII administered over the course of treatment was 142,200 units (range: 57,600 to 246,400). One patient (UPN≠2) subsequently received prolonged low-dose PFVIII in an effort to induce immune tolerance, after bleeding had resolved. The median duration of hospitalization was 28 days (range: 8–96).

Six of seven patients received concurrent immunosuppressive therapy with corticosteroids and oral cyclophosphamide (1.5–2.5 mg/kg/day). Three patients also received intravenous doses of cyclophosphamide and methotrexate and one received vincristine. Three patients received IV IgG, though this was without clear effect (Fig. 1).

Hemostatic levels of FVIII (>0.5 U/ml) were achieved in 6 of 7 patients at a median time of 12.5 hr (range: 4–96) and maintained for the initial 6 days, following combined bolus and continuous infusion PFVIII (Fig. 1). One patient (UPN ≠1) who had received PFVIII in the preceding 4-month period, did not achieve therapeutic levels of FVIII (peak FVIII: 0.08 U/ml). The remaining patients reached a mean peak FVIII level of 1.29 U/ml (range: 0.54–1.75) during continuous infusion PFVIII.

In four (UPN≠2,3,6,7) of the six patients who achieved hemostatic FVIII levels, FVIII declined abruptly to less than one-half of the preceding days' values between day 7 and 11 while on continuous infusion PFVIII therapy. To control the sudden decrement in FVIII, plasmapheresis was instituted in these patients. The number of plasmaphereses ranged from two to five. Following plasmapheresis, all patients received a bolus dose of PFVIII and the continuous infusion was resumed. The three patients with autoantibodies achieved therapeutic FVIII levels after plasmapheresis, whereas the one patient with hemophilia did not (UPN≠2). In one other patient (UPN ≠5), plasmapheresis was instituted early (day 4), before any decline in FVIII levels were noted.

Thirteen surgical procedures were performed to control bleeding during continuous infusion PFVIII. In addition, seven central venous catheters were inserted to gain venous access and to permit plasmapheresis. All patients achieved good hemostasis with prompt control of the initial bleeding site, except for one patient (UPN≠7) who was subsequently shown to have a surgical cause for bleeding, and in whom hemostasis was delayed until definitive surgical correction could be performed. No patient died.

In patients with autoantibodies, immunosuppressive therapy was maintained for a mean duration of 162 days (range: 120–180). No relapses were seen in this group of patients after a median follow-up of 581 days (range: 348–1,206). All patients with autoantibodies have normal FVIII plasma levels at the time of this report, with no evidence of inhibitors.

Adverse Effects

Two patients experienced chills and back pain (UPN ≠2, 7) during the initial bolus of PFVIII, which resolved readily with intravenous administration of diphenhydramine HCl. Anaphylaxis did not occur during the course of this study. However, one patient (UPN ≠2) who was subsequently re-exposed to PFVIII 2 years later (at a time when his antiporcine inhibitor titer had declined to 0.8 BU) developed a full anaphylactic reaction, requiring resuscitation, despite premedication with corticosteroids.

Four patients developed thrombocytopenia during continuous infusion PFVIII. These were the same patients who had developed resistance to the infused PFVIII. Platelet counts declined in these patients from the normal range to nadir counts of 11–87 $\times 10^9$/L between days 18 and 24 following the start of continuous infusion PFVIII, although counts began to drop in each case after 7 to 12 days of infusion. All patients who developed thrombocytopenia had received concurrent cyclophosphamide, three had received plasmapheresis, and two had concomitant major bleeds. PFVIII was discontinued in three of four patients and immunosuppression was decreased in three patients. Platelet transfusions were required only in the patient with the platelet count of 11 $\times$ 10^9/L. Platelet counts normalized in all patients within 2.5–7 days after stopping PFVIII.

Description of the Clinical Courses of the Patients

Time-course diagrams (Fig. 1) show the therapy given (FVIII dosage as well as immunosuppressants administered), the response in terms of plasma FVIII level, and the platelet count for each patient. Data on presentation are shown in Table I. Additional clinical details are presented below.

UPN ≠1 was a 46-year-old man with severe hemophilia A and high-titre inhibitors (previous peak titres of >400 B.U. against both human and porcine FVIII). He had been given PFVIII by bolus injection 4 months previously for treatment of a retroperitoneal bleed. On this

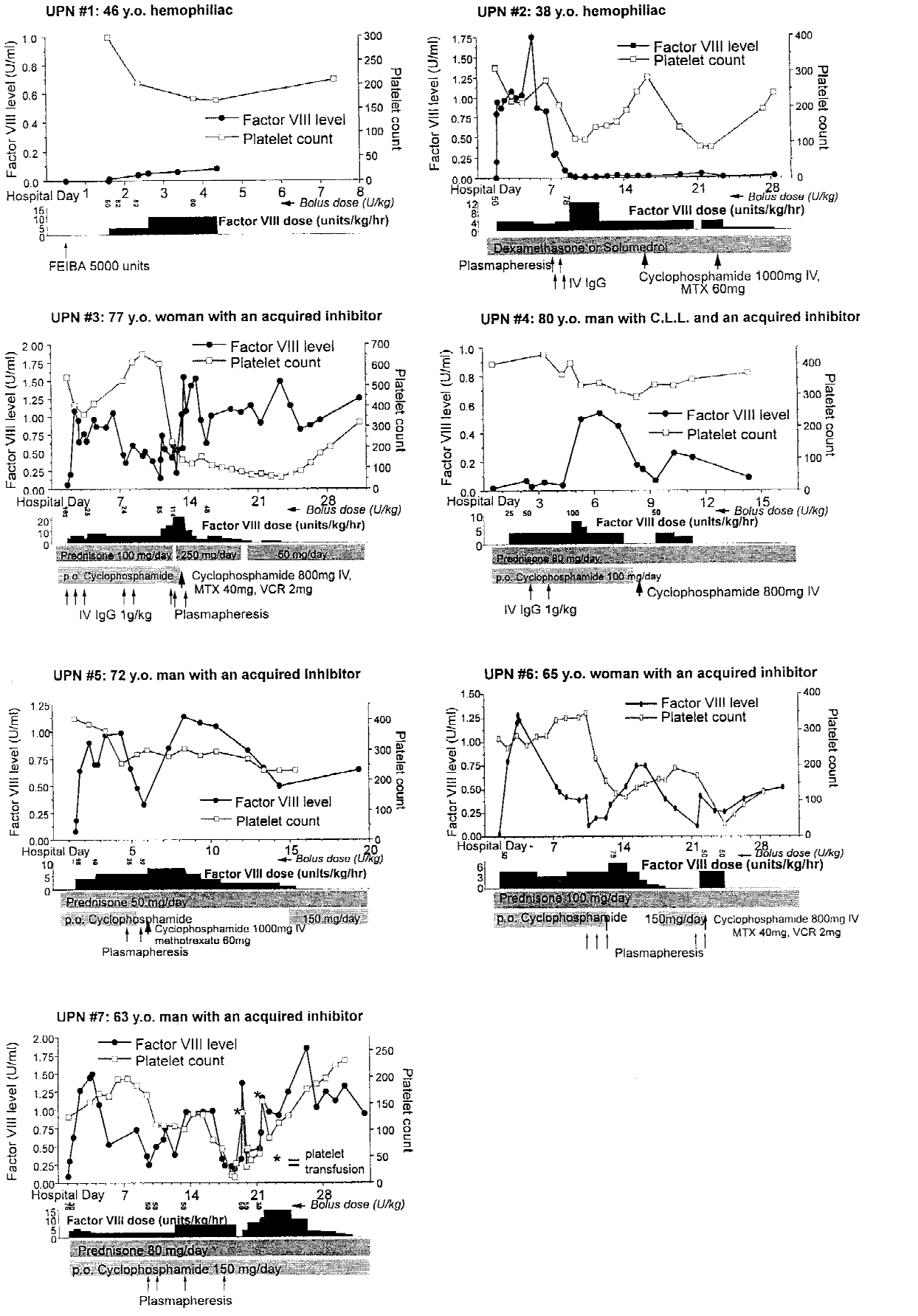

Fig. 1. Clinical courses of the patients. See text for details.

occasion, he presented with hematemesis and melena, and CT scanning demonstrated bleeding into the mesentery and the lumen of the small bowel. Although the peak FVIII level achieved with PFVIII infusion was only 0.08 U/ml, the intestinal bleeding was controlled and the patient was discharged after 5 days. Inhibitor titres measured 3 weeks later were 35 BU and 31 BU to human and porcine FVIII, respectively.

UPN #2 was a 38-year-old man with severe hemophilia A and a high-responding inhibitor. He presented with sudden back pain, weakness, and numbness in the lower extremities; MRI revealed a spinal subdural hematoma at the level of C2–T9. Dexamethasone was given along with PFVIII, and a central line was inserted while the FVIII level was therapeutic. On day 7, a sudden drop in the FVIII level occurred, which was not responsive to an increase in the PFVIII infusion, IV IgG, plasmapheresis, or the subsequent administration of cytotoxic agents. On day 22 the platelet count fell (without concomitant leukopenia), and the PFVIII infusion was decreased to 0.8 U/kg/hr on the following day. With this, the platelet count recovered. The infusion was continued at this low dose for an additional 82 days in an attempt to induce immune tolerance; however, at day 105 the inhibitor titres had risen to 140 BU and 85 BU against human and porcine FVIII, respectively, and the low-dose infusion was stopped.

The patient received recombinant FVIIa and ε-aminocaproic acid from day 68 to 70 to control a new right knee bleed, with good effect. He was discharged from hospital on day 98, with improvement of the leg weakness following a rehabilitation program, though he was still unable to walk.

UPN #3 was a 77-year-old woman who was admitted to a peripheral hospital for an upper gastrointestinal bleed. She was previously healthy. An arterial puncture was complicated by a right forearm compartment syndrome, and she was transferred to our center. Prior to transfer, she had received activated prothrombin complex concentrate (FEIBA®, Immuno Canada, Toronto), 90 U/kg every 12 h for 6 doses, without control of the bleeding. Fasciotomy was performed on days 2 and 5 to relieve the compartment syndrome, without bleeding complications. On day 7, a marked drop in the plasma FVIII level was noted, and IV IgG was given with temporary improvement although levels fell again by day 10. This responded to plasmapheresis, cytotoxic therapy, and a brief increase in the PFVIII infusion; the infusion was subsequently tapered off with maintenance of a normal FVIII level. It should be noted that the platelet count fell sharply on day 12, and then declined further until day 23, at which time the PFVIII was stopped completely with subsequent recovery of the platelet count.

Cyclophosphamide was given for 6 months, and FVIII levels have been normal with no evidence of an inhibitor in 1,206 days of follow-up. Neurological compromise from the compartment syndrome persists.

UPN #4 was an 80-year-old man with a diagnosis of chronic lymphocytic leukemia (Rai stage 0; lymphocyte count 5.1×10^9/L with normal red cell and platelet counts), on no therapy. He presented with multiple large ecchymoses over the right groin and left lower leg. A therapeutic FVIII level was achieved by day 5, and clinical improvement in the bleeding diathesis was noted. Starting on day 8, cyclophosphamide was given intravenously every 2 weeks, which was continued for 6 months. No further bleeding occurred, and the plasma FVIII level recovered gradually; it was 0.18 U/ml on day 75 (with an inhibitor titre of 3 BU), and 0.72 U/ml on day 166 (with no inhibitor detectable). No recurrence of the inhibitor or progression of the CLL has been observed in 910 days of follow-up.

UPN #5 was a 72-year-old man with a history of ischemic heart disease and compensated hypothyroidism. He presented with swelling, pain, and erythema of the right elbow. Aspiration was attempted, but was complicated by an extensive hematoma. Subsequently, large ecchymoses developed on the left shoulder, right lower leg, and left thigh. A therapeutic FVIII level was achieved quickly, and the ecchymoses resolved. A central venous line was inserted on day 3 to permit plasmapheresis (the drop in FVIII level in days 5 and 6 was presumed to be due to removal of the infused product during pheresis). Cyclophosphamide was continued for 6 months, and no relapse of the inhibitor has been seen during a follow-up of 637 days.

UPN #6 was a 65-year-old woman with a history of Graves disease. She presented with a 2-week history of bruising and an incipient compartment syndrome due to a right forearm bleed. With PFVIII therapy, the bruising subsided, as did the swelling in the right arm, and a fasciotomy was not required. A subclavian central venous catheter was inserted on day 4, without complications, because of poor venous access and anticipation of plasmapheresis.

The FVIII level fell on day 8, but responded temporarily to plasmapheresis, cytotoxic agents, and an increased dose of PFVIII. The platelet count fell shortly thereafter, but rallied as the PFVIII infusion was tapered. It fell again when the PFVIII infusion was resumed, reaching a nadir of 35×10^9/L, but recovered when the PFVIII was stopped. Oral cyclophosphamide was continued for 5 months. Her FVIII level has exceeded 1.0 U/ml since day 43, with 581 days follow-up.

UPN #7 is a 63-year-old man, previously well, who presented at a peripheral hospital with epistaxis, bruising of the left arm, hematuria, and difficulty voiding. Despite a preoperative aPTT of 42 sec, a transurethral prostatectomy was performed, which was followed by profuse hematuria. He was transferred to this hospital. Despite

the fact that hemostatic levels of FVIII were achieved rapidly with PFVIII infusion, bleeding continued. Cystoscopic exploration did not stop the bleeding. On day 17, both the FVIII level and the platelet count declined precipitously; the platelets reached a nadir of 11×10^9/L on day 18. On day 19, in preparation for a repeat exploratory cystoscopy, 12 U of platelets were given, and replacement FVIII therapy was changed to recombinant human factor VIII (Kogenate®, Miles Inc., Elkhart, IN), with which a hemostatic level was achieved. Urological bleeding was finally controlled surgically on day 21. No further bleeding complications or relapses occurred during the follow-up period of 348 days.

DISCUSSION

In this study we have demonstrated that continuous infusion PFVIII is a simple and highly effective treatment for patients with inhibitors to FVIII. Hemostatic levels of FVIII were achieved rapidly with bolus PFVIII and steady therapeutic levels of FVIII were maintained for up to 6 days with continuous infusion of PFVIII. This allowed us to achieve prompt control of bleeding in our patients. The stable infusion rates and plasma FVIII levels simplified monitoring and allowed emergency surgical procedures to be carried out as required. The one patient (UPN≠1) in whom hemostatic levels were not achieved had previously been exposed to PFVIII, and had a high anti-porcine inhibitor titer at the start of treatment. There were no deaths in our patients, although a mortality rate of 15% has previously been reported for acquired inhibitors (see reference [20]).

Although the initial hemostatic response was excellent, a sudden fall in the plasma level of FVIII occurred at days 7 to 11 in four patients, despite the continued infusion of PFVIII. This decrease in FVIII levels was likely related to an increase in the activity of anti-porcine FVIII antibodies. This phenomenon has previously been observed; an anamnestic response to PFVIII was noted in 71% of hemophiliac patients with inhibitors [10] and in 15% of patients with acquired inhibitors [18]. In our study we observed a beneficial effect of plasmapheresis in those patients with autoantibodies, who had developed an anamnestic response, and similar results were reported by Hambley et al. [19]. However, other authors have not observed this effect [20]. An alternative therapy for bleeding patients with an anamnestic response to FVIII is the use of prothrombin complex concentrates [8], or recombinant factor VIIa [9,21,22]. Rarely, DDAVP may be used when the inhibitor level titres are low (<5 BU) [23].

A delayed complication of continuous infusion PFVIII is thrombocytopenia, which was noted in 4 of our 7 patients, all of whom had received at least 18 days of therapy. It has previously been observed that the platelet count can fall following the administration of PFVIII [10]. Hay et al. have observed a slight fall in the platelet count following single treatments with PFVIII, but this thrombocytopenia was mild and transient, and usually of no clinical significance. The drop was dose related and, rarely, severe thrombocytopenia was seen in an unspecified number of patients after ''intensive'' therapy [10]. The high incidence of thrombocytopenia in our study is likely related to the high doses of PFVIII in conjunction with prolonged duration of treatment. In addition, other factors may have contributed to the fall in the platelet counts; most of the patients had received myelosuppressive therapy and plasmapheresis and some were actively bleeding when the thrombocytopenia developed. Nonetheless, the recovery of platelet counts with the discontinuation of PFVIII suggests that PFVIII was a significant contributory factor to the thrombocytopenia. In each case, thrombocytopenia occurred several days after resistance to PFVIII infusion developed, raising the speculation that a drug-immune mechanism may be responsible for the late-occurring thrombocytopenia. Whether the severity of thrombocytopenia with PFVIII is influenced by the mode of administration, i.e., bolus vs. continuous infusion, is unknown.

Other side-effects of PFVIII infusion were minimal. We encountered only two mild transfusion reactions, a low rate that may be attributable to the fact that all patients received corticosteroids from the onset. Various rates of reported transfusions reactions range from 2.3% [10] to 50% [24]. Of greater concern, however, was the development of anaphylaxis in one patient (UPN≠2) who was later re-exposed to PFVIII and whether this is a common phenomenon remains to be determined. However, none of the patients who had autoinhibitors required retreatment, and there were no recurrences in these patients after a median follow-up of 581 days. We believe that aggressive and prolonged immunosuppression with cyclophosphamide contributed to this favorable result, and this conclusion is supported by other reports [25,26].

CONCLUSIONS

This study confirms the feasibility and efficacy of continuous infusion PFVIII in the management of patients with FVIII inhibitors. Hemostasis can be readily achieved and maintained for the first 6 days of treatment. After that time, FVIII levels may fall and plasmapheresis or other therapies may then be required. Prolonged infusions of PFVIII may be associated with thrombocytopenia, but this is readily reversible with discontinuation of treatment.

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